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PATENT SPECIFICATION

(11)

126929]

1269291

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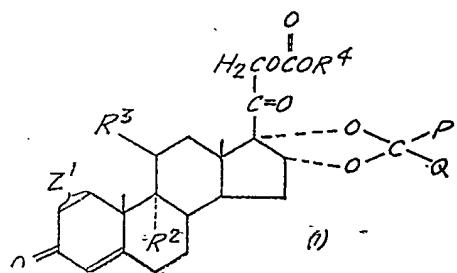
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(54) IMPROVEMENTS IN OR RELATING TO CORTICOID CARBONATES

(71) We, SYNTEX CORPORATION, a Panamanian Corporation of Apartado Postal 7386, Panama, Panama, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

5 This invention relates to novel cyclopentanophenanthrene derivatives. More particularly, this invention is directed to 21-corticoid carbonates which can be represented by the following general formula: 5



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ERRATA

SPECIFICATION No. 1,269,291

Page 4, line 24, for cyclopropyl read cyclo-
 propylethyl 15
 Page 5, line 3, for *p*-chlororopipophenone read
p-chloropropiophenone
 Page 5, line 24, for determind read determined 20

THE PATENT OFFICE
 14th June 1972

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positions comprising compounds of formula 1 in some cases

The term "lower alkyl" and derivations thereof appearing in the above definitions and elsewhere in the instant specification denote alkyl groups containing 1 to 6 carbon atoms, inclusive, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, amyl, hexyl, and the like. The term "cycloalkyl" denotes cycloalkyl groups having from 3 to 10 carbons such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, 3-(cyclohexyl)-

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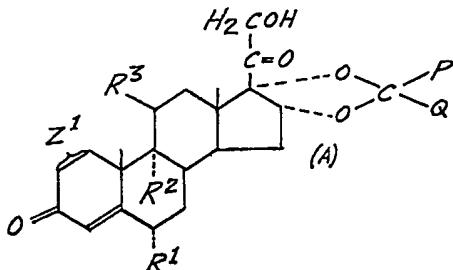
[Price 25p]

SEE ERRATA SLIP ATTACHED

propyl, and the like. The term "aralkyl" and derivations thereof appearing in the above definitions and elsewhere in the instant specification denote phenylalkyl and substituted phenylalkyl groups containing from 7 to 10 carbon atoms, inclusive, such as benzyl, *o*-, *m*- and *p*-methylbenzyl, phenylethyl and 3-(phenyl)propyl.

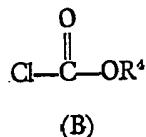
5 The compounds of Formula I are prepared according to this invention by reacting a steroid of the general formula

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wherein R¹, R², R³, P, Q and Z¹ are as previously defined with a chloroformate having the general formula:

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wherein R⁴ is as previously defined. The steroid of Formula A can be reacted in a pyridine solution with the chlorocarbonate of Formula B in excess of one mole of the steroid. The reaction can be conducted in the presence of a cosolvent such as chloroform, dichloromethane, monoglyme, or tetrahydrofuran since the neat pyridine solution may cause some decomposition of certain of the reactants. The reaction is

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conducted at a temperature of from -70° to 20°C, for from 5 to 48 hours, preferably for 18 hours at 0°C, and purified by conventional procedures. For example, the reaction mixture containing the product carbonate can be diluted with water, filtered, and the solid product dried and purified by crystallization or chromatography on silica gel to yield the 21-corticoid carbonates of Formula I.

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The chloroformates of Formula B together with representative procedures for reacting them with steroids are disclosed in U.S. Patents 3,056,727, 3,314,856, 3,329,570, 3,409,641 and Belgium Patent 706,333. In general, the chloroformates are formed by reacting a corresponding alcohol with an excess of phosgene in a suitable inert organic solvent to obtain the chlorocarbonate. For example, phosgene can be allowed to bubble for a period of 1.5 hours into 120 cc. of anhydrous ethanol cooled to 0°C. Then 30 g. of cyclohexylmethanol is introduced. The reaction mixture is then agitated at 0°C for a period of 24 hours, the phosgene is removed by bubbling nitrogen therethrough, and the mixture is concentrated to dryness under vacuum to yield the cyclohexylmethyl chloroformate.

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Other suitable chloroformates include methyl chloroformate, ethyl chloroformate, n-propyl chloroformate, cyclohexyl chloroformate and benzyl chloroformate.

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The compounds of Formula A are described together with methods for their preparation in U.S. Patent 3,053,838. Among the suitable starting steroids useful in the process of this invention can be mentioned the 16 α ,17 α -acetal derivatives of

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6 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione,
6 α -chloro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione,
6 α ,9 α -difluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione,
6 α ,9 α -dichloro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione,

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6 α -chloro-9 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione,
9 α -chloro-6 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregn-4-ene-3,20-dione,
6 α ,9 α ,11 β -trichloro-16 α ,17 α ,21-trihydroxypregn-4-ene-3,20-dione,
9 α ,11 β -dichloro-6 α -fluoro-16 α ,17 α ,21-trihydroxypregn-4-ene-3,20-dione,
6 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregna-1,4-diene-3,20-dione,
6 α -fluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregna-1,4-diene-3,20-dione,
6 α ,9 α -difluoro-11 β ,16 α ,17 α ,21-tetrahydroxypregna-1,4-diene-3,20-dione,

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5 $6\alpha,9\alpha$ -dichloro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione,
 6 α -chloro- 9α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione,
 9 α -chloro- 6α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione,
 6 $\alpha,9\alpha,11\beta$ -trichloro- $16\alpha,17\alpha,21$ -trihydroxypregna-1,4-diene-3,20-dione, and
 9 $\alpha,11\beta$ -dichloro- 6α -fluoro $16\alpha,17\alpha,21$ -trihydroxypregna-1,4-diene-3,20-dione,
 5 with lower alkanals such as paraldehyde, propanal, and hexanal; halogenated lower
 alkanals such as chloral hydrate trifluoroacetaldehyde hemiacetal and hepta fluoro-
 10 butanal ethyl hemiacetal; di(lower alkyl)ketones, such as acetone, diethylketone, di-
 butylketone, methylethylketone, and methylisobutylketone; halogenated di(lower alkyl)-
 15 ketones, such as 1,1,1-trifluoroacetone; cycloalkanones, such as cyclopentanone, cyclo-
 hexanone, suberone, cyclobutanone, and cyclodecanone; mono- and dicycloalkyl
 20 ketones, such as cyclohexylmethyl ketone and dicyclopropyl ketone; monocyclic aromatic aldehydes, such as benzaldehyde, halobenzaldehydes (e.g. *p*-chlorobenzaldehyde and *p*-fluorobenzaldehyde), lower alkoxy benzaldehydes (e.g. α -anisaldehyde), di(lower alkoxy)benzaldehydes (e.g. veratraldehyde), hydroxybenzaldehydes (e.g. salicylaldehyde), dihydroxybenzaldehydes (e.g. resorcylaldehyde), lower alkyl benzaldehydes (e.g. *m*-tolualdehyde and *p*-ethylbenzaldehyde), di(lower alkyl)benzaldehydes (e.g. *o,p*-dimethylbenzaldehyde), nitrobenzaldehydes, acylamidobenzaldehydes (e.g. *N*-acetyllantranildaldehyde), and cyanobenzaldehydes; monocyclic aromatic lower
 25 alkanals, such as phenylacetaldehyde, α -phenylpropionaldehyde, β -phenylpropionaldehyde, γ -phenylbutyraldehyde, and aromatically-substituted halo, lower alkoxy, hydroxy, lower alkyl, nitro, acylamido and cyano derivatives thereof; monocyclic heterocyclic aldehydes, such as picolinaldehydes, furfural, thiophene carbonals and halo, lower alkoxy, hydroxy, lower alkyl, nitro, and cyano derivatives thereof; monocyclic heterocyclic lower alkanals; monocyclic aromatic lower alkyl ketones, such as acetophenone, propiophenone, butyrophenone, valerophenone, iso-caprophenone, halophenyl lower alkyl ketones (e.g. *p*-chloroacetophenone and *p*-chloropropiophenone), (lower alkoxy)phenyl lower alkyl ketones (e.g. *p*-anisyl methyl ketone), di(lower alkoxy)phenyl lower alkyl ketones, hydroxyphenyl lower alkyl ketones, dihydroxphenyl lower alkyl ketones (e.g. resacetophenone), (lower alkyl)phenyl lower alkyl ketones (e.g. methyl *p*-tolyl ketone, di(lower alkyl)phenyl lower alkyl ketones (*o,p*-xylyl methyl ketone), nitrophenyl lower alkyl ketones (e.g. *p*-nitroacetophenone), acylamidophenyl lower alkyl ketones (e.g. acetyl anilines), and cyanophenyl lower alkyl ketones; benzophenone, and mono or bis substituted halo, lower alkoxy, hydroxy, lower alkyl, nitro, acylamido and cyano derivatives thereof; monocyclic aromatic lower alkanones, such as 1-phenyl-3-butanone and 1-phenyl-4-pentanone, and aromatically substituted derivatives thereof; monocyclic heterocyclic ketones, such as 2-acetyl furan, 2-benzoylfuran, and 2-acetylthiophene; monocyclic heterocyclic lower alkanones; and monocyclic heterocyclic ketones, such as alloxan.

40 EXAMPLE 1
 40 Ethyl chloroformate (1 ml.) is added to a solution of $6\alpha,9\alpha$ -difluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione $16\alpha,17\alpha$ -acetonide (500 mg.) in pyridine (15 ml.) at 0°C. The reaction mixture is maintained at 0°C for 18 hours, poured into water, filtered, washed with water, and crystallized from acetone-hexane to yield $6\alpha,9\alpha$ - difluoro - $11\beta,16\alpha,17\alpha,21$ - tetrahydroxypregna - 1,4 - diene - 3,20 - dione $16\alpha,17\alpha$ -acetonide 21-ethyl-carbonate.

50 EXAMPLE 2
 50 Repeating the procedure of Example 1 with
 50 6α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-4-ene-3,20-dione $16\alpha,17\alpha$ -acetonide,
 50 6α -chloro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-4-ene-3,20-dione $16\alpha,17\alpha$ -acetonide,
 55 $6\alpha,9\alpha$ -difluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-4-ene-3,20-dione $16\alpha,17\alpha$ -acetonide,
 55 $6\alpha,9\alpha$ -dichloro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-4-ene-3,20-dione $16\alpha,17\alpha$ -acetonide,
 55 6α -chloro- 9α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-4-ene-3,20-dione
 60 $16\alpha,17\alpha$ -acetonide,
 60 9α -chloro- 6α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-4-ene-3,20-dione
 60 $16\alpha,17\alpha$ -acetonide,
 60 $6\alpha,9\alpha,11\beta$ -trichloro- $16\alpha,17\alpha,21$ -trihydroxypregna-4-ene-3,20-dione $16\alpha,17\alpha$ -acetonide,

$9\alpha,11\beta$ -dichloro- 6α -fluoro- $16\alpha,17\alpha,21$ -trihydroxypregn-4-ene-3,20-dione
 $16\alpha,17\alpha$ -acetonide,
 6α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione $16\alpha,17\alpha$ -
5 acetonide,
 6α -chloro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione $16\alpha,17\alpha$ -
 acetonide,
 6α -chloro- 9α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione
 $16\alpha,17\alpha$ -acetonide,
 9α -chloro- 6α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione
10 $16\alpha,17\alpha$ -acetonide,
 $6\alpha,9\alpha,11\beta$ -trichloro- $16\alpha,17\alpha,21$ -trihydroxypregna-1,4-diene-3,20-dione
 $16\alpha,17\alpha$ -acetonide, and
 $9\alpha,11\beta$ -dichloro- 6α -fluoro- $16\alpha,17\alpha,21$ -trihydroxypregna-1,4-diene-3,20-dione
15 $16\alpha,17\alpha$ -acetonide,
 yields the corresponding 21-ethyl carbonates. 15

EXAMPLE 3

Repeating the procedures of Examples 1 and 2 but replacing ethyl chloroformate with methyl chloroformate, n-propyl chloroformate, n-pentyl chloroformate, cyclopropyl chloroformate, cyclopentyl chloroformate, cyclohexyl chloroformate, cyclopropylethyl chloroformate, cyclopentylmethyl chloroformate, cyclohexyl ethyl chloroformate, benzyl chloroformate, and *p*-methylbenzyl chloroformate yields the corresponding 21-methyl carbonate, 21-(n-propyl)carbonate, 21-(n-pentyl)carbonate, 21-cyclopropyl carbonate, 21-cyclopentyl carbonate, 21-cyclohexyl carbonate, 21-cyclopropyl carbonate, 21-cyclopentylmethyl carbonate, 21-cyclohexylethyl carbonate, 21-benzyl carbonate, and 21-(*p*-methylbenzyl)carbonate of 20
 6α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregn-4-ene-3,20-dione $16\alpha,17\alpha$ -acetonide,
 6α -chloro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregn-4-ene-3,20-dione $16\alpha,17\alpha$ -acetonide,
 $6\alpha,9\alpha$ -difluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregn-4-ene-3,20-dione $16\alpha,17\alpha$ -
30 acetonide,
 $6\alpha,9\alpha$ -dichloro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregn-4-ene-3,20-dione $16\alpha,17\alpha$ -
 acetonide,
 6α -chloro- 9α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregn-4-ene-3,20-dione
 $16\alpha,17\alpha$ -acetonide,
 9α -chloro- 6α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregn-4-ene-3,20-dione 35
35 $16\alpha,17\alpha$ -acetonide,
 $6\alpha,9\alpha,11\beta$ -trichloro- $16\alpha,17\alpha,21$ -trihydroxypregn-4-ene-3,20-dione $16\alpha,17\alpha$ -
 acetonide,
 $9\alpha,11\beta$ -dichloro- 6α -fluoro- $16\alpha,17\alpha,21$ -trihydroxypregn-4-ene-3,20-dione
 $16\alpha,17\alpha$ -acetonide,
 6α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione $16\alpha,17\alpha$ -40
40 acetonide,
 6α -chloro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione $16\alpha,17\alpha$ -
 acetonide,
 $6\alpha,9\alpha$ -difluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregna-1,4-diene-3,20-dione 45
45 $16\alpha,17\alpha$ -acetonide,
 6α -chloro- 9α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregn-1,4-diene-3,20-dione
 $16\alpha,17\alpha$ -acetonide,
 9α -chloro- 6α -fluoro- $11\beta,16\alpha,17\alpha,21$ -tetrahydroxypregn-1,4-diene-3,20-dione
 $16\alpha,17\alpha$ -acetonide,
 $6\alpha,9\alpha,11\beta$ -trichloro- $16\alpha,17\alpha,21$ -trihydroxypregn-1,4-diene-3,20-dione 50
50 $16\alpha,17\alpha$ -acetonide, and
 $9\alpha,11\beta$ -dichloro- 6α -fluoro- $16\alpha,17\alpha,21$ -trihydroxypregn-1,4-diene-3,20-dione
 $16\alpha,17\alpha$ -acetonide. 50

EXAMPLE 4

Following the procedure of Example 1, 21-ethylcarbonates of $6\alpha,9\alpha$ - difluoro- $11\beta,16\alpha,17\alpha,21$ - tetrahydroxypregn - 1,4 - diene - 3,20 - dione $16\alpha,17\alpha$ - acetals, wherein the $16\alpha,17\alpha$ -acetal groups are acetals of propanal, hexanal, chloral hydrate, trifluoroacetaldehyde hemiacetal, hepta fluorobutanal ethyl hemiacetal, acetone, diethylketone, dibutylketone, methylethylketone, methylisobutylketone, 1,1,1-trifluoroacetone, cyclopentanone, cyclohexanone, suberone, cyclobutanone, cyclodecanone, cyclohexylmethylketone, dicyclopentylketone, benzaldehyde, *p*-chlorobenzaldehyde, *p*-fluorobenzaldehyde, α -anisaldehyde, veratraldehyde, salicylaldehyde, *m*-tolualdehyde, *p*-ethylbenzaldehyde, *o,p*-dimethylbenzaldehyde, phenylacetaldehyde, α -phenylpro- 55
55 60

5 pionaldehyde, β -phenylpropionaldehyde, picolinaldehyde, furfuraldehyde, acetophenone, propiophenone, butyrophenone, valerophenone, isocaprophenone, *p*-chloroacetophenone, *p*-chlororopiphenone, *p*-anisyl methyl ketone, methyl *p*-tolyl ketone, α, p -xylyl methyl ketone, benzophenone, 1-phenyl-3-butanone, 1-phenyl-4-pentanone, 2-acetyl furan, 2-benzoylfuran, 2-acetylthiophene, and alloxan are obtained from the corresponding 21-hydroxy compounds.

EXAMPLE 5

10 Improved anti-inflammatory activity of the compounds of this invention is demonstrated as follows. A "rat-ear" test was used to compare the anti-inflammatory activity of $6\alpha, 9\alpha$ -difluoro- $11\beta, 16\alpha, 17\alpha, 21$ -tetrahydroxypregna-1,4-diene-3,20-dione-
16 $\alpha, 17\alpha$ -acetonide 21-ethylcarbonate (Compound A) with $6\alpha, 9\alpha$ -difluoro- $11\beta, 16\alpha, 17\alpha, 21$ -tetrahydroxypregna-1,4-diene-3,20-dione $16\alpha, 17\alpha$ -acetonide (Compound B) the latter compound being a commercial anti-inflammatory compound having the generic name fluocinolone acetonide.

15 The test is a modification of a method originally described by Tonelli, et al in Endocrinology 77, 625 (1965). A vehicle consisting of 20% pyridine, 5% distilled water, 74% diethyl ether and 1% croton oil is used. Intact male 21-day-old rats are anesthetized, and the test compound is inuncted onto the ear as follows: 0.05 ml. is inuncted onto the inside of the left ear and 0.05 ml. is inuncted onto the outside of
20 the left ear. The vehicle containing the irritant is given simultaneously with the anti-inflammatory compound. Rats in a control group receive only the vehicle. Both ears are removed 6 hours after administration of the compound, and pieces of uniform size are punched out with a No. 4 cork borer. The pieces of ear are then weighed and the difference in weight increase between the two pieces of ear are determined.

25 The data obtained is summarized in Table 1 showing the activity in comparison with the activity of hydrocortisone.

Table 1

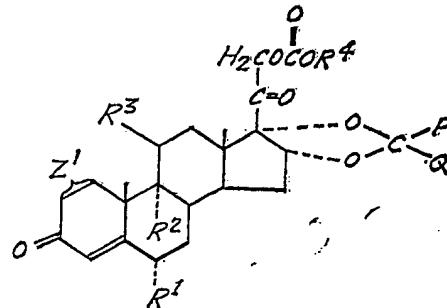
Compound	No. of rats	Dose range tested, μ g.	Activity ^(a)
A	84	0.1 — 2.7	390
B	235	0.05 — 2.7	150

^(a) hydrocortisone has an activity value of one.

As can be readily seen from the data in Table 1, as measured by the rat-ear test, the 21-ethylcarbonate is 2.6 times as active as the corresponding 21-hydroxy compound.

35 WHAT WE CLAIM IS:—

1. A compound of the formula:



wherein

40 R¹ is fluoro or chloro;

R² is hydrogen, fluoro or chloro;

R³ is hydroxy or when R² is chloro, R³ can be chloro;

R⁴ is lower alkyl, cycloalkyl or aralkyl;

P and Q are hydrogen, lower alkyl, halogenated lower alkyl, monocyclic cycloalkyl, monocyclic aryl, monocyclic aryl lower alkyl, monocyclic heterocyclic

45 or monocyclic heterocyclic lower alkyl or together with the carbon atoms to which they are joined P and Q are cycloalkyl or monocyclic heterocyclic and

Z^1 is a single or double bond.

2. A compound of Claim 1 wherein R^4 is methyl, ethyl, n-propyl, cyclohexyl, or cyclohexylmethyl.

3. A compound of Claim 1 wherein R^4 is lower alkyl.

4. A compound of Claim 3 wherein P and Q, together with the carbon atom to which they are joined are cyclopentyl or cyclohexyl.

5. A compound of Claim 4 wherein R^2 is hydrogen.

6. A compound of Claim 4 wherein R^2 is fluoro.

7. A compound of Claim 3 wherein P and Q are methyl.

10 8. A compound of Claim 7 wherein R^2 is hydrogen.

9. As a compound of Claim 8, 6α - fluoro - $11\beta,21$ - dihydroxy - $16\alpha,17\alpha$ - isopropylidenedioxypregn - 4 - ene - 3,20 - dione 21-ethyl-carbonate.

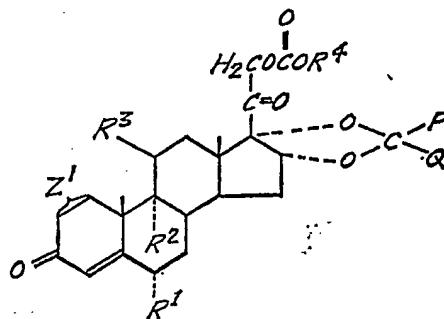
10 10. As a compound of Claim 8, 6α - fluoro - $11\beta,21$ - dihydroxy - $16\alpha,17\alpha$ - isopropylidenedioxypregna - 1,4 - diene - 3,20 - dione 21-ethylcarbonate.

15 11. A compound of Claim 7 wherein R^2 is fluoro.

12. As a compound of Claim 11, $6\alpha,9\alpha$ - difluoro - $11\beta,21$ - dihydroxy - $16\alpha,17\alpha$ - isopropylidenedioxypregn - 4 - ene - 3,20 - dione 21-ethylcarbonate.

13. As a compound of Claim 11, $9\alpha,11\beta$ - dichloro - 6α - fluoro - 21 - hydroxy - $16\alpha,17\alpha$ - isopropylidenedioxypregna - 1,4 - diene - 3,20 - dione 21-ethylcarbonate.

20 14. The process for the preparation of a 21-carbonate ester of the general formula:



wherein

R^1 is fluoro or chloro;

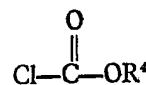
25 R^2 is hydrogen, fluoro or chloro;

R^3 is hydroxy or when R^2 is chloro, R^3 can be chloro;

R^4 is lower alkyl, cycloalkyl or aralkyl;

30 P and Q are hydrogen, lower alkyl, halogenated lower alkyl, monocyclic cycloalkyl, monocyclic aryl, monocyclic aryl lower alkyl, monocyclic heterocyclic or monocyclic heterocyclic lower alkyl or together with the carbon atom to which they are joined P and Q are cycloalkyl or monocyclic heterocyclic, and Z^1 is a single or double bond;

which comprises reacting together a corresponding 21-hydroxy starting steroid, and a chloroformate of the formula:



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wherein R^4 is lower alkyl, cycloalkyl, or aralkyl.

15. A compound according to Claim 1 substantially as herein described and exemplified.

16. Process according to Claim 1 substantially as herein described and exemplified.

40 17. A 21-carbonate ester having the general formula as defined in Claim 14 when obtained by the process claimed in Claim 14 or Claim 16.

18. A therapeutic composition comprising a compound as claimed in any one of Claims 1 to 13 or Claim 15, or Claim 17 and a pharmaceutical excipient.

19. Therapeutic composition according to Claim 18 substantially as herein described.

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